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Credentialing for Breast Lymphatic Mapping: How Many Cases Are Enough?

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Objective
To evaluate credentialing issues for sentinel lymphatic mapping for breast cancer.

Summary Background Data
The sentinel lymph node (SLN) is defined as the first lymph node receiving lymphatic drainage from a tumor. The SLN accurately reflects the status of the axillary nodes in patients with early-stage breast cancer, and SLN mapping is gaining widespread acceptance. Few of the many published feasibility studies of lymphatic mapping for breast cancer have adequate numbers to assess credentialing issues for this new procedure.

Methods
Five hundred consecutive SLN biopsies were performed at one institution, over a 20-month period, by eight surgeons, using isosulfan blue dye and technetium-labeled sulfur colloid. The authors reviewed each surgeon's success rate in finding the SLN, and false-negative rate, relative to level of experience with the technique.

Results
Lymphatic mapping performed by an experienced surgeon (surgeon A, B, or C) was associated with a higher success rate (94%) than when it was performed by one with less experience (86%). Ten failed mapping procedures occurred in the first 100 cases. For each of the ensuing 100 cases, there were eight, six, six, and four failed mapping procedures, suggesting that increasing experience does not eradicate failed mapping procedures completely. The false-negative rate among 104 patients in whom axillary dissection was planned in advance was 10.6% (5/47). Most false-negative results occurred early in the surgeon's experience: when the first six cases of every surgeon were excluded, the false-negative rate fell to 5.2% (2/38).

Conclusions
With increasing experience, failed SLN localizations and false-negative SLN biopsies occur less often. Combined dye and isotope localization, enhanced histopathology, a backup axillary dissection, and judicious case selection are required to avoid the high false-negative rate of one's early experience.

The histologic status of the axillary nodes remains the single best predictor of survival in patients with breast cancer.[1,2] The sentinel lymph node (SLN) is defined as the first lymph node in a regional lymphatic basin that receives lymph flow from a primary tumor.[3,4] It can be detected by the injection of radiocolloid (first reported by Krag et al[5]), blue dye (first reported by Giuliano et al[6]), or both (first reported by Albertini et al[7]). A total of 18 series of SLN biopsies have been published, 10 using isotope[5,8–16] (n = 1367), 4 using blue dye[6,17–19] (n = 484), and 4 using isotope plus blue dye[7,20–22] (n = 196) in 2047 patients, all validated by an axillary dissection. These studies collectively confirm that the SLN can be identified in 93% of cases, and that it correctly predicts axillary node status in 98% of all patients and 94% of node-positive cases. A false-negative SLN biopsy is of the utmost concern, potentially resulting in either axillary relapse or incorrect decisions about systemic treatment. The aim of this study was to establish (for individual surgeons at one institution) the success rate in finding the SLN and the false-negative rate in relation to the surgeon's level of experience with the technique.

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Table 1. RESULTS OF LYMPHATIC MAPPING

	No. of Patients	%
Total cases performed	500	100
DCIS cases excluded	8	2
Total evaluable cases	492	98
Successful mappings	458	92
Failed mappings	34	7

DCIS, ductal carcinoma *in situ*.

Table 2. SUCCESSFUL SLN MAPPINGS, BY SURGEON

	Total SLN Procedures	
Surgeon	No. Done	Failed Mappings
A	145	10 (7%)
B	185	7 (4%)
C	84	6 (7%)
D	45	4 (8%)
E–H	33	7 (21%)

PATIENTS AND METHODS

Patients

In a prospective study from September 1996 to May 1998, 500 patients with clinical T1–3N0 breast cancer had SLN biopsy at Memorial Sloan-Kettering Cancer Center. The first 60 procedures were performed under a formal institutional review board protocol and have been reported previously.[21] The first 500 procedures are the subject of a separate detailed analysis.[23] All patients had biopsy-proven malignancy and clinically negative axillae. Mastectomy and breast-conservation patients were equally eligible. Eight patients were excluded because final pathology revealed only ductal carcinoma *in situ* with no evidence of invasive carcinoma, resulting in a study population of 492 (Table 1).

The methods used for lymphatic mapping and pathologic analysis were detailed in previous reports.[21,23] In brief, SLN biopsy was performed at one institution by eight surgeons using isosulfan blue dye and technetium-labeled sulfur colloid. We reviewed each surgeon's success rate in finding the SLN (number of successful localizations divided by number of total procedures) and false-negative rate (number of false-negative procedures divided by number of node-positive cases) relative to level of experience with the technique.

A successful SLN biopsy was defined as a lymph node with visible blue staining. Successful radioisotope localization required that the ratio of *ex vivo* SLN isotope counts to postexcision axillary bed counts be at least 4. For all procedures in which the SLN was not identified, a conventional axillary dissection was done.

Statistics

Statistical analysis of unsuccessful mapping procedures was calculated using Fisher's exact test. The statistical package Instat 2.0 (Graphpad software) was used for the analyses.

RESULTS

The mean patient age was 56 years (range 21 to 87). Three surgeons performed 84% of the cases, and the remaining five surgeons performed an average of 16 cases each. In 7% of cases (n = 34), the SLN was not identified. The SLN was successfully identified by blue dye in 80% (393/492), by isotope in 85% (419/492), and by the combination of blue dye and isotope in 93% (458/492) of the 492 evaluable patients.

Lymphatic mapping performed by a surgeon experienced with the technique (surgeon A, B, or C) was associated with a higher success rate (94%) than when performed by one with less experience (86%, Table 2) ($p = 0.012$, Fisher's exact test). Ten failed mapping procedures occurred in the first 100 cases. For each 100 of the ensuing cases, there were eight, six, six, and four failed procedures, suggesting that increasing experience does not eradicate failures completely.

In 104 cases, the surgeon had planned before surgery to perform an axillary dissection, regardless of SLN histology. Of these 104 cases, 47 were node-positive and 5 did not have malignancy detected in the SLN, for a true false-negative rate of 10.6% (5/47). Most false-negative cases occurred early in each surgeon's experience (Table 3). When the first six cases of every surgeon were excluded, the false-negative rate fell to 5.2% (2/38); eliminating the first 15 cases of each surgeon would further reduce the false-negative rate to 2%.

All false-negative cases were carefully reviewed. Three of the five false-negative SLN biopsies could be described as technical failures on the part of the surgeon. Cases #272

Table 3. FALSE-NEGATIVE SLN MAPPINGS, BY SURGEON

	SLN Procedures with Planned ALND*		
Surgeon	No. Done	False-Negative Rate	Case No.
A	21	1/13 (8%)	1
B	35	1/14 (7%)	6
C	15	1/5 (20%)	12
D	26	1/12 (8%)	20
E–H	7	1/3 (33%)	3

* Planned ALND, backup axillary lymph node dissection planned in advance.

and #418 involved a mapping procedure in patients with a large upper outer quadrant biopsy cavity encompassing a substantial portion of the tail of the breast. In case #349, the postexcision axillary bed counts were higher than the counts from the *ex vivo* SLN, suggesting the presence of additional SLNs that were not pursued. The remaining two false-negative cases occurred very early in our experience (#3 and #11), when our technique was evolving.

DISCUSSION

The SLN accurately reflects the status of the axillary lymph nodes in most patients with breast cancer, and for those with early-stage disease it is rapidly emerging as an alternative to conventional axillary dissection. Although SLN biopsy for breast cancer may be considered state-of-the-art in experienced hands, information on credentialing for this new procedure is scarce. Morton et al's classic 1992 report[4] of SLN biopsy for melanoma clearly documents a learning curve for the procedure; higher-volume surgeons found the SLN more often, and each surgeon's success rate improved with experience. There were only two false-negative procedures, precluding analysis of the learning curve in these terms. Giuliano's work reflects the developmental stage of blue dye SLN mapping for breast cancer, with successful SLN localizations increasing from 65%[6] to 93%[17] over a personal experience of hundreds of cases. Most false-negative results occurred in earlier patients.

Krag et al's multicenter validation study,[15] which reports on isotope-guided SLN biopsy for breast cancer as performed by 11 surgeons at 11 different institutions, is more discouraging. Although SLNs were found in 93% of 443 cases (range 82% to 98%), false-negative results occurred in 11.4% of 114 node-positive cases (range 0% to 28.6%). Successful SLN localization was more frequent for high-volume surgeons, as expected, but the false-negative rate was unrelated to surgical experience: indeed, one of the three highest-volume surgeons also had the highest false-negative rate (28.6%).

Our data clearly demonstrate a learning curve for SLN biopsy as well. Successful SLN localization increased with experience, from 90% in the first 100 cases to 96% in the fifth 100. False-negative results appeared to diminish with experience, although firm conclusions are limited by the small number ($n = 5$) of false-negative cases involved. Our experience, and that of the cumulative literature to date, would suggest that the false-negative rate for SLN biopsy (with experience) is closer to 5% than to 10%.

Several strategies will minimize the incidence of failed and false-negative procedures as one is learning to perform SLN biopsy:

1. Using isotope and blue dye combined for localization
2. Using enhanced histopathologic analysis of the SLN
3. Relying on a backup axillary dissection early in one's experience
4. Limiting SLN biopsy without axillary dissection to patients with a lower likelihood of axillary metastases.

Our initial success with SLN biopsy was enhanced by the combined use of isotope and blue dye for localization,[21] following the protocols developed by Krag et al,[5] Giuliano et al,[6] and Albertini et al.[7] This synergy has continued over our first 500 procedures.[23] Although most SLNs were found by both dye and isotope, approximately 10% have been found by either dye or isotope alone. More importantly, approximately 10% of the positive SLNs have been found by dye or isotope alone; these would have been missed by relying on a single technique of localization. Despite increasing success with each method individually, we plan to continue with a combined approach to SLN localization.

Enhanced histopathology with serial sectioning of the SLN and staining for both hematoxylin/eosin and cytokeratins allows the detection of micrometastatic disease that would have been missed by routine single-section analysis of the axillary nodes. Giuliano et al[24] clearly documented the efficacy of enhanced pathology for examination of the SLN in breast cancer. Their yield of positive axillary nodes increased from 29% (in 134 axillary dissection patients with conventional pathology) to 42% (in 162 comparable-stage patients who underwent SLN biopsy with enhanced pathology). They further demonstrated that among 60 patients with negative SLNs by both hematoxylin/eosin and immunohistochemistry, only 1 of 1087 non-SLNs (0.09%) subjected to the same intensive level of scrutiny proved to be positive.[25] There were three false-negative SLN biopsy procedures in our first 60 cases, based on routine single-section pathologic analysis of the SLN,[21] and one of these proved to be positive on retrospective study with serial sections and immunohistochemistry. Enhanced pathologic examination has subsequently become our routine for all patients whose SLNs prove negative on frozen section.

A backup axillary dissection is an essential element in learning to perform SLN biopsy. In no other way can the individual surgeon or institution compare results with those obtained elsewhere and precisely audit the false-negative procedures. The technique for SLN biopsy continues to evolve, and with sufficient experience it may eventually be possible to define specific aspects of SLN localization that predict a highly accurate outcome regardless of the surgeon's experience. This is not yet the case. With a cumulative experience of 1000 SLN biopsies, we continue to see a low but definite incidence of false-negative procedures, and we continue to perform SLN biopsy with backup axillary dissection for most T2 cancers and for any procedure in which the findings are in any way ambiguous or uncertain.

The final element in minimizing the false-negative rate is case selection. Based on our initial study of 60 patients,[21] in which SLN biopsy accurately predicted the axillary node status in 43/44 T1 patients, we began to offer SLN-negative T1 patients the option of no axillary dissection. We have observed no false-negative SLNs for T1a,b breast cancers

(≤1.0 cm), nor have others.[8] The ideal patient for SLN biopsy alone has a low likelihood of axillary metastases, either by virtue of small tumor size or favorable histopathology (medullary, tubular, or colloid cancers); in this setting, the accuracy of SLN biopsy should be ≥99%. Subsequent relapse in the regional node basin, reported to occur in 4% of patients with melanoma after a negative SLN biopsy result,[26] has not yet been reported in patients with breast cancer. As experience and follow-up accumulate, such recurrences will happen. With adherence to the above guidelines, our hope is that this risk will be comparable to that after a conventional axillary dissection (≤1%).

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Discussion

DR. KIRBY I. BLAND (Providence Rhode Island): As stated, the histologic status of the axillary lymphatics continues as the most important prognostic variable in breast cancer, and is the principal determinant of clinical management. Twenty-two years ago, Cabanas proposed the term "sentinel node" for the lymphatic tissue that first receives drainage from a primary tumor. He suggested that examination of this tissue after its removal with limited surgery may single out those individuals in whom more extensive lymphadenectomy should be performed. As indicated in this presentation, the seminal work by Morton, Guiliano, Alex, Krag, and Albertini has defined more precisely state-of-the-art applications of sentinel lymph node biopsy, which is incorporated in the injections of sulfur-radiocolloid or lymphozurin-blue dye or the combination of these two modalities.

The authors state that in many studies, including the present one, surgeons experienced in these methods can identify the sentinel node with success rates that approach 95%. I commend the authors for achieving a 92% success rate in lymphatic mapping. However, the false-negative sentinel lymph node biopsy is of the greatest concern, as the omission of definitive therapy, for example, axillary sampling, irradiation, and/or systemic therapy, may result in the potential enhancement of locoregional failure and reduction in overall survival. The authors investigated the failed mappings in seven patients, 21% of 33 total SLN procedures. These seven failed mappings were performed by the four surgeons with the least experience with lymphatic mapping, and the highest frequency of false-negative results (33%). Thus, failed localizations and false-negative biopsies lessen in number as the surgeon's experience increases. Despite the pundits in many institutions calling for the use of single techniques, we, like you, will continue to use combined approaches for nodal sampling, as some failures will occur with either technique.

So, Pat, I have several questions for you.

It is well known that older patients are less able to retain radioactive colloid because their lymph nodes have been replaced by fat as they age. So increasing the volume of the diluent and the concentration or volume of the tracer isotope can increase uptake within sentinel nodes by a factor of 10 and may offset this problem. What are your thoughts on the influence of patient age on the success rate of the methods?

Secondly, others have noted, as have we, that false-negative results occur most commonly when the index tumor is in the lateral one-half of the breast. Further, with tumors that are contiguous to lymphatic basins, technical isolation either with a blue dye or radioisotope can be problematic. In our experience, the combination technique is essential for upper outer quadrant lesions, especially those in the axillary tail and the upper outer quadrant, and I think this is where the radionuclide can best differentiate the index tumor from the lymphatics.

You indicate a similar problem with identification of the nodes in two of your five false-negative cases, and a third false-negative in your series appears to have resulted because of the presence of additional sentinel nodes in the sample. Can you convey to us how you can actually sort out this technical problem and how have you done this in your future analysis, now that you have a much larger database?

Third, your manuscript suggests now that you are at 800 and you just told us you have gone to 1000 total nodal basins. Please convey to this audience what you would consider now as the favorable lesion that you would not do the sentinel node biopsy—for instance, the T1a or T1b lesion with favorable histology low-grade or histopathology such as a medullary, tubular, or colloid carcinoma. Would you omit a back-up axillary dissection in those patients?

And I think the bottom line of this paper is the last question I would have. There are a number of community surgeons in this audience, Pat. Please tell us, based on the numbers that you have presented, a credentialing guideline for the number of sentinel lymph node procedures that community surgeons could currently perform and feel comfortable without doing the back-up axillary dissection. Is it 10? It sounds like that is the number you have arrived upon in your final presentation today.

Dr. David S. Robinson (Kansas City, Missouri): Nationally, the concept of sentinel lymph node biopsy has quickly captured the attention of surgeons in a number of different venues, and now it appears that it is becoming mature in the area of breast disease.

The thesis presented here involves the idea of a learning curve in the acquisition of a new skill. Others have looked at this in their collective data.

This is a slide on loan to me from Doug Berenkin from the University of South Florida, Tampa, which reflects something very similar to what Dr. Borgen has shown us. This is the learning curve experience of five surgeons looking at lymphatic mapping specifically in breast disease, looking at the failure rate on the vertical curve, the number of cases on the horizontal curve. The mean is the yellow curve somewhat in the middle. And their suggestion, after looking at this very carefully, is that it all begins to dampen out somewhere around 25 to 30 cases.

Drs. Cox, Krag, Guiliano, and others recently met with the American Society of Breast Surgeons at the time of the American College of Surgeons (meeting) and discussed their criteria for performing sentinel lymph node biopsy without a complete axillary lymph node dissection. They suggested that one should document an experience of over 30 cases with sentinel lymph node biopsy followed by complete axillary lymph node dissection and that there should be an 85% or greater success rate in identifying the sentinel lymph node in the axilla. They suggested a false-negative rate of less than 5%, or 10 consecutive cases of sentinel lymph node biopsy demonstrating metastatic disease without a false-negative lymph node. And they also suggested that if one finds one in that series that the 10 starts over.

Other issues remain, though, and your paper helps a great deal to elucidate them. At this time in the United States, there is no standard for the preparation of technetium sulfur colloid, the particle size, how we inject it, the volume of the injectate, the timing of the blue dye injection at the time of open cavity, and how we use the technique of the wand. So it becomes really somewhat of an issue of how such a rate of either institutional variability might occur. Would you care to comment on that, please?

And having used both techniques, the dual and hot blue dye techniques, I know that once a hot node has been discovered, there is less enthusiasm to go ahead and look for the blue. Do you go ahead and open up the incision widely?

Philosophically, I agree with you that the technique best serves the patient with a small T1 or T2 cancer, but paradoxically, these very patients are the ones likely not to have very much in the way of nodal disease.

In your series, at least in the printed format, 492 sentinel lymph node biopsies were performed. One hundred and four completed axillary dissection. Forty-seven had nodal positivity and there were five false-negatives, one for each of five of the eight surgeons. When you get down to the bottom line, Dr. Borgen, this doesn't seem like the numbers are very great. Do you think that we can actually make the decision about 10 on the learning curve based on this information? And would you please tell us, what about the other 388 patients? Do you think that a completion dissection would serve them?

And, finally, from a philosophical position, after we go to a great deal of length to bring down the local amount of breast disease to a low level, perhaps as low as 2% with radiation therapy and a wide excision, there is still a 5% false-negative rate. Are we justified in doing a sentinel lymph node biopsy at this time without a completion axillary dissection?

Dr. Edward M. Copeland, III (Gainesville, Florida): I commend Dr. Borgen and coauthors for properly reporting their false-negative rate. Five of 104 patients with axillary dissection had a false-negative result, meaning the sentinel node was negative, but positive nodes were found in the axillary dissection specimen. This false-negative rate could have been reported as 4.8% (5 of 104 axillary dissections), but more properly is reported as 10.6%, or five negative sentinel lymph nodes out of 47 positive axillary dissections.

As most of us are unwilling to leave axillary nodes intact for T1 breast cancers, with the risk of axillary metastasis reported to be from 7% to 18%, why would we be willing to accept a 10.6% risk of unrecognized axillary metastasis in patients with sentinel lymph node biopsy?

Dr. Borgen has shown that unrecognized axillary metastasis falls to 5.2% with experience. What the group at Memorial Sloan-Kettering must decide is if this retained axillary metastasis rate is acceptable. If the answer is yes, then the group should be willing to leave the axilla untouched for a T1a lesion, since the chance of axillary metastasis for lesions of this size is between 5% and 7%.

In fact, in my practice to date, I have only been willing to accept the sentinel node as accurate without a back-up axillary dissection for T1 lesions or those lesions with extensive intraductal carcinoma in situ for which the possibility of microinvasion exists. If I do have any false-negative results, then my chance of harm is minimized, since the chance of axillary metastasis in these circumstances is low.

General surgeons derive a significant portion of their practice income from operations on the breast, just as they do from operations on the gallbladder. Consequently, sentinel lymph node biopsy may have a similar impact on a general surgeon's practice as laparoscopic cholecystectomy did. If this is the case, all general surgeons are going to become eager to develop expertise in the technique of sentinel node biopsy. I would suggest that sentinel lymph node biopsy and laparoscopic cholecystectomy as new techniques are not parallel circumstances. If laparoscopic cholecystectomy fails, the surgeon can recover by doing an open cholecystectomy. Likewise, in only rare instances is the gallbladder malignant.

On the other hand, failure to identify the proper sentinel lymph node does run a real risk of leaving undetected metastasis in the axilla, which will go unrecognized for several months or possibly years until the disease becomes manifest by clinical examination. If you are one who feels that axillary dissection provides some survival benefit for those who have positive nodes, then the patient will be denied this opportunity. Also, the patient will be improperly staged, and the decision of adjuvant therapy will be made without all available pathologic information.

DR. PATRICK I. BORGEN (Closing Discussion): Relative to Dr. Bland's question about patient age, we have not performed a true multivariate analysis controlling for age. We have not, however, in looking at the data set, observed a higher failure rate in older patients, even though you may predict that based on the fatty replacement. We have observed that the soil on which these cells land is important. We are most concerned about the lymph node that is totally replaced with breast cancer, where there is probably little or no lymphatic flow. And this node may be a source of some of our false-negatives.

The sage advice is, after the sentinel lymph node is out, to take your finger—an important scientific instrument—and feel in the axilla and feel if you feel a rock remaining. I think that remains a useful test in today's age.

Tumors in the upper outer quadrant of the breast, which is where 80% of breast cancers occur, can be quite problematic. The radiation scatter area from the tracer injection site can completely obliterate the axilla, and in those cases the blue dye is particularly useful.

With respect to the question about a favorable lesion, we have not begun abandoning a back-up axillary node dissection in T2 lesions. We still do it if there is lymphatic invasion of high-grade T1 lesions. So a favorable lesion would be a T1a/b, selected T1c's, colloid mucinous medullary, tubular, the other favorable types of breast cancer, we are willing to forgo the axilla node dissection. At the end, I will talk about the question about the total number of cases that should be done.

Dr. Robinson's question about blue dye plus tracer, I think that what we may be looking at here is simply broadening the throw of our net. The median number of sentinel lymph nodes in most series is between one-and-a-half and two-and-a-half lymph nodes, and it may be that the different particle size in blue dye *versus* the tracer may simply broaden the throw of our net.

I want to finish on two important points that the reviewers raised. One is, aren't these small numbers? And the answer is yes. Sentinel node mapping is a work in progress. However, our experience, if published tomorrow, would represent about 20% of the existing literature on sentinel node mapping. I think we have to play the clues as we get them. To me, the message here is not the magic cutoff of 10 or 15 or 20, but the sobering realization that false-negatives occur. To the surgeons who are out there thinking of buying a gamma probe and doing sentinel mapping without a back-up node dissection, I would think that this would be sobering.

And, finally, how can we accept the technology that we admit has a true false-negative rate of 5%? And I think that each of the three reviewers very correctly raised some concern about that. I think, fundamentally, it comes down to what is your goal in doing an axillary node sampling or an axillary node dissection or a sentinel lymph node biopsy. If your goal is accuracy, we know that if we hand our pathologist 21 lymph nodes, their published known error rates are between 5% and 10%. This beats that.

If your goal is identifying node-positive patients for systemic therapy, in every reported series, sentinel lymph node biopsy patients, when compared to standard axillary node dissection patients, have a higher node positivity rate by tumor size. We are finding more node-positive patients with sentinel lymph node mapping, and this undoubtedly has to do with not only the accuracy of the technique, but the level of pathologic sectioning and scrutiny that these nodes are subjected to.

And, finally, if your goal is removing cancer, then, yes, in 5% of your node-positive patients you are going to be leaving cancer behind in 1% to 2% of all your patients. And so it comes down to a risk/benefit analysis. Does the reduced morbidity, does the elimination of general anesthesia, the elimination of a surgical drain, elimination of a hospital stay, does the identification of more node-positive patients, do these factors provide the justification of a means to an end with respect to sentinel lymph node biopsy? And I would submit to you today that this question lies at the heart of the future of sentinel lymph node mapping.